Randomised clinical trial: a liquid multi-strain probiotic vs. placebo in the irritable bowel syndrome – a 12 week double-blind study

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SUMMARY

Background
The importance of interactions between the host and gut microbiota in the pathogenesis of irritable bowel syndrome (IBS) is becoming increasingly apparent. Probiotics offer a potential new treatment for IBS, but current results are conflicting, largely as a result of poorly designed trials and non-standardisation of outcome measures.

Aim
To assess the efficacy of a liquid, multi-strain probiotic (Symprove) in IBS.

Methods
A single-centre, randomised, double-blind, placebo-controlled trial of adult patients with symptomatic IBS. Patients received 12 weeks of treatment with the probiotic or placebo (1 mL/kg/day). The primary efficacy measure was the difference in change in the IBS symptom severity score (IBS-SSS) between probiotic vs. placebo at week 12. Secondary outcome measures included change in the IBS quality of life (IBS-QOL) score and change in the IBS-SSS symptom component scores.

Results
A total of 186 patients were randomised and 152 patients completed the study. The mean change in IBS-SSS was −63.3 probiotic vs. −28.3 placebo. The mean difference in the IBS-SSS was statistically significant [−35.0 (95% CI; −62.03, −7.87); P = 0.01]. There was no significant improvement in the IBS-QOL. No serious adverse events were reported.

Conclusions
The multi-strain probiotic was associated with a statistically significant improvement in overall symptom severity in patients with IBS, and was well tolerated. These results suggest this probiotic confers benefit in IBS and deserves further investigation (ISRCTN identifier: 77512412).

Aliment Pharmacol Ther
INTRODUCTION

Irritable bowel syndrome (IBS) is one of the most common gastrointestinal conditions with an estimated prevalence of between 10% and 20% in most countries. Estimates of prevalence can differ greatly because of different diagnostic criteria used. In general, the looser the criteria, the higher the prevalence. Accordingly, in the UK, the prevalence of IBS is reported to be 12% using Rome II diagnostic criteria and 22% using Manning criteria.

Irritable bowel syndrome is characterised by abdominal pain or discomfort and a clustering of other symptoms of varying type and severity including bloating and alterations in bowel function with episodes of diarrhoea and/or constipation. Although many consider IBS to be purely a gastrointestinal condition, it is increasingly apparent that extra-intestinal symptoms including genitourinary, musculoskeletal (fibromyalgia, arthralgia, backache), headaches and fatigue, menstrual and sexual dysfunction, and anxiety and mood disorders are frequently present. Taken collectively, the symptoms of IBS may impact significantly on quality of life (QOL) and result in substantial increased direct health care costs, as well as indirect costs such as absenteeism from work. The health utility of severe IBS [where utility is a measure of health-related QOL on a scale of 0 (death) to 1 (perfect health)], was found to be 0.7 in one recent analysis, which is similar to that of Class 3 congestive heart failure and rheumatoid arthritis. The majority of patients with IBS self-medicate with over the counter preparations or are managed by primary care physicians; only the more severe cases are referred for specialist opinion and management. Most treatment options for IBS (antispasmodics, laxatives, obstipants, anti-depressants, etc.) focus on the management and control of symptoms; however, their efficacy is often limited or unproven.

There has been a renewed interest in recent years into understanding the pathophysiological mechanisms and aetiology of IBS. This has resulted in new insights, which highlight the importance of interactions between the host and intestinal luminal microbial and nonmicrobial constituents. Both qualitative and quantitative differences have been found in the gut luminal microbiota (using gene cloning and sequencing techniques) between healthy control subjects and patients with IBS. Accordingly, new therapeutic options that have the potential to alter intestinal bacterial composition and their metabolic products, including, dietary manipulation [such as a low fermentable oligo-, di- and mono-saccharides, and polys (FODMAP) diet], antibiotics (such as rifaximin) and probiotics have been tested.

The use of probiotics in particular has become the subject of much interest, some of which is fuelled by the popular press, holistic ‘natural health’ groups and the dairy industry. In addition, there is increasing interest in research that aims to establish both the mechanisms of action of different probiotic strains as well as their efficacy in the treatment of IBS. The possible mechanisms of action of different probiotic strains include effects on intestinal motility, visceral hypersensitivity, secretion of interleukins (e.g. IL-10) and increases in anti-inflammatory T-cell populations. To date, clinical trials with probiotics in the treatment of IBS have yielded conflicting data and frequently suffered from significant methodological limitations. The vast majority of these trials were not considered of sufficient quality to be included in two recent meta-analyses, or to support valid health claims to the standards required by food standard agencies. However, despite the methodological limitations of many of these trials, both meta-analyses concluded that probiotics may be of benefit in the treatment of IBS. What does seem to be clear from the literature is that the efficacy of individual probiotics depends both on the strain(s) of bacteria and the formulation of the preparations and/or delivery methods used.

Symprove is a liquid-based, multi-strain, gluten-free probiotic. It contains four bacterial strains suspended in a liquid extract of barley as a delivery medium. The live bacteria within the delivery media have been shown, in in vitro testing, to be resilient to an environment equivalent to human gastric physiological resting activity (pH 3). Our study was designed to assess the efficacy of this probiotic preparation in a randomised, double-blind, placebo-controlled trial, in patients with symptomatic IBS.

METHODS

Study design and participants

This was a single-centre, randomised, double-blind, placebo-controlled trial designed to investigate the efficacy and safety of the probiotic in the treatment of gastrointestinal symptoms in patients with IBS. The trial took place at King’s College Hospital, London, between October 2008 and June 2011.

Patients with IBS were recruited for the study from Kings College Hospital Outpatients Department and
local general practitioner (GP) practices. Patients recruited from the Outpatient Department at King’s College Hospital had a diagnosis of IBS of sufficient severity to have been referred from primary care for confirmation of diagnosis and/or treatment. Patients from local GP practices, all of whom had been seen by a gastroenterologist, were identified from practice databases and sent information leaflets about the study along with invitations to join.

The study was designed to include men and women aged between 18 and 65 years who had not benefited from conventional treatments for IBS (mebeverine, buscopan, dietary change, laxatives, obstipants, etc.). The upper age limit was decided on in order to minimise the number of patients with age-related organic diseases (such as diverticular disease) and avoid patients on multiple medications that can lead to IBS-like symptoms. All patients had a diagnosis of IBS as defined by Rome III criteria and were symptomatic at study entry. Only patients with an IBS-symptom severity score (SSS) of ≥150 were eligible for the study. This level was chosen to ensure that patients were at least symptomatic and that it would be possible to detect a ‘clinically important’ change in the IBS-SSS of ≥50 as defined by the original authors of this scale.24 Patients with all sub-types of IBS, based on prominence of stool symptoms, were included in the study. This decision was made to attempt to capture all patients with IBS in this phase II study, including those with mixed symptoms who do not fall either into the diarrhoea or into the constipation subtypes.

The probiotic used has never been studied formally in a cohort of patients with IBS. It was therefore felt that including more patients in the probiotic arm (2:1) would yield more information about potential tolerance and side effects associated with this probiotic while controlling the cohort size for practical purposes as a single-centre study.

Patients with organic gastrointestinal conditions were excluded from the study. These were ruled out by a combination of investigations including full blood count, C reactive protein (CRP), erythrocyte sedimentation rate (ESR), coeliac serology, renal and liver function tests, intestinal permeability and faecal calprotectin. Furthermore, all patients with increased intestinal permeability or increased faecal calprotectin and those aged over 40 years who had not undergone a colonoscopy in the preceding 5 years underwent colonoscopy and where indicated, wireless capsule endoscopy. Exclusion criteria also included previous intolerance and/or adverse reactions to probiotics or the use of these products within the preceding 1 month, pregnancy or lactation, major systemic disease (e.g. heart failure, renal failure, malignant tumours, liver cirrhosis, etc.), previous or current significant psychiatric co-morbidity, current or previous (within the last 5 years) drug or alcohol misuse or dependency, regular antibiotic usage, current use of a low FODMAP diet or ineligibility as judged by a senior trial physician. Concurrent IBS medication and/or wheat and dairy exclusion diets were permitted if started more than 3 months previously and if the patient agreed to not change dosing regimens or diets during the study.

Study protocol
Patients who fulfilled the inclusion criteria and agreed to participate were randomised into three equal sized groups using a two-stage computerised randomisation protocol. Two groups received the probiotic and one the placebo, giving an overall treatment to placebo ratio of 2:1. Blinding of allocation to study medication was maintained until the completed study database was locked and passed to the study statistician. The duration of the study was 12 weeks with three reviews at 4-weekly clinic visits. An untreated follow-up to week 16 was included in the study design and patients were re-assessed at the end of this period. Compliance was assessed at each study visit, with patients asked whether they had missed; ‘no doses’, ‘less than one dose/week’, ‘one to three doses/week’, or ‘more than three doses/week’.

Study medication
Symprove (Symprove Ltd, Farnham, Surrey, UK) contains four strains of naturally occurring beneficial bacteria: Lactobacillus rhamnosus NCIMB 30174, Lactobacillus plantarum NCIMB 30173, Lactobacillus acidophilus NCIMB 30175 and Enterococcus faecium NCIMB 30176. The bacteria are in a water-based suspension of barley extract with each 50 mL dose containing ten billion live bacteria. The placebo was a similar liquid in appearance and taste, containing inert flavourings and water only and was supplied by the probiotic manufacturer. The placebo and probiotic were packaged in identical sealed boxes, identified by a trial batch/code number only. Patients were instructed to keep study medications refrigerated (between 2 °C and 7 °C) throughout the study and to self-administer 1 mL/kg each morning on an empty stomach. Food and fluids were allowed 20 min later. Missed doses could be taken later in the day provided no food had been consumed during the preceding 2 h.
Clinical outcomes
The primary efficacy measure was the difference in change in overall symptom severity between the two groups as measured by the IBS-SSS\textsuperscript{24} from baseline to week 12. This is a validated illness-specific rating scale, which provides a composite score of patients’ assessment of severity of four symptoms, namely; abdominal pain (two measures), abdominal distension, satisfaction with bowel habit and to what degree the symptoms affect or interfere with QOL. The questions in the IBS-SSS relate to individual domains for abdominal pain, bloating, satisfaction with bowel habit and overall interference with QOL. The collective scores to these individual domains give rise to the total score. The IBS-SSS total score ranges from 0 to 500; a higher score indicating worse condition. Scores below 175 represent mild IBS, 175–300 represent moderate severity, and scores above 300 represent severe IBS.

Secondary outcome measures were change in IBS-QOL\textsuperscript{25} score from baseline to week 12; change in IBS-SSS component scores at week 12; changes in IBS-SSS and IBS-QOL between week 12 and 16. The IBS-QOL scale range is from 0 to 100, a higher number indicating better QOL. This scale evaluates 34 broad well-being issues including feelings of dysphoria, sexual relationships, social issues, body image, etc.

Assessment of safety and tolerability included the reporting of any treatment adverse events.

In our original protocol, change in IBS-QOL was the primary efficacy measure. Secondary outcome measures were changes in the IBS-SSS total score and changes in symptom component scores. This original protocol was then amended so that change in global IBS-SSS became the primary outcome measure, and change in the IBS-QOL was included as a secondary end-point. These changes were made in the light of further discussions which suggested that measurement of symptomatic responses would be more appropriate for this phase II study. These changes were made prior to study entry.

The proportions of patients achieving mild or no symptoms and those achieving minimal clinically important differences (MCID) from baseline to week 12 were calculated in post hoc analyses. The MCID was defined by the original authors of the IBS-SSS as a change of \( \geq 50 \) points\textsuperscript{24} and by a later group as \( \geq 95 \) points.\textsuperscript{26} As far as we are aware these are the only definitions of MCID for IBS in the literature.

Laboratory measures
Haematological and biochemical tests were carried out using Adviva 1200 and 2400 analysers, respectively (Siemens, Frimley, UK). Intestinal permeability assessment (differential urinary excretion of lactulose/L-rhamnose) using mass spectrometry for marker analyses and faecal calprotectin (EK-Cal Calprotectin Kit, Buhmann, Switzerland) measurements were carried out by the Department of Clinical Biochemistry, King’s College Hospital as previously described.

Ethics issues
The study was conducted in accordance with the guidelines for Good Clinical Practice (CPMP ICH 135 95), the principles of the Declaration of Helsinki and with all relevant local and national guidelines including the archiving of records. All patients were provided with written and verbal information about the study and subsequently gave informed consent before study entry.

The Medicines and Healthcare products Regulatory Agency was consulted prior to starting this study and concluded that Symprove is classified as a food supplement rather than an investigational medicinal product.

The National Research Ethics Service, Outer South East London Committee approved the study protocol. Further review was undertaken locally by the Research and Development Committee of King’s College Hospital who acted as Sponsors for the study. The study was registered on the ISRCTN register (International Standard Randomised Controlled Trial Number) (ISRCTN77512412). Subsequent changes to the ISRCTN entry were made to reflect changes to the study protocol. All changes to the study protocol were made prior to the study opening.

Statistical analysis
Statistical analysis was conducted using \textsc{stata} 12.1\textsuperscript{29} and \textsc{spss} 19 statistical software.\textsuperscript{30}

The total number of patients for inclusion in the study was initially derived based on response defined as an improvement of \( \geq 50 \) points in the global IBS-SSS, with an assumption that 40% of patients in the placebo arm would show a \( \geq 50 \) point improvement (i.e. reduction) and 65% of patients in the probiotic arm would show a similar improvement. The size of the sample needed was calculated as 186, detected with a power of 90%, \( \alpha = 5\% \). Prior to commencement of the trial, a change of \( \geq 50 \) points as a binary outcome was altered because it was felt that there was insufficient evidence from the literature to support the use of this change as a robust primary end-point. Given the exploratory nature of the study, as a first of its kind, it was felt that a comparison of the difference in mean SSSs between the two groups at the end of treatment and follow-up would be
more appropriate. The cohort size was not changed, but the power was subsequently recalculated based on the observed difference in mean SSS after treatment to ensure that study power was reported accurately. This resulted in the final study having a power of 80% using the above assumptions. Frequency tables and cross-tabulations were derived to explore any differences or associations between different variables and/or baseline characteristics.

The efficacy measures were analysed for the per-protocol (PP) and on an intention-to-treat (ITT) basis using independent sample t-test and analysis of covariance. The PP population included all patients that received the full 12 weeks of study medication. The ITT population included all patients that received any study medication. The last observation carried forward (LOCF) methodology was used to generate missing data in the ITT. The ITT population analysis based on the LOCF was compared to the PP (complete case analysis) as a sensitivity analysis of the methodology used.31

Pearson’s chi-squared analysis was used to compare the proportions of patients achieving mild or no symptoms and those achieving minimal clinically important difference (MCID) in post hoc analyses. Pearson’s chi-squared analysis was also used to investigate any differences in withdrawals at weeks 12 and 16.

Modelling with ordinary linear regression to adjust for baseline symptom severity, age and gender were also performed. Residual plots were used to test the regression models. A P value at or below 0.05 was considered as a statistically significant result.

RESULTS

From October 2008 to September 2011, 392 patients were screened for the study. A total of 201 patients who were screened were not recruited; of these, 50 did not have a diagnosis of IBS confirmed; a further 52 patients did not consent to take part; 39 did not attend a follow-up screening visit. Forty one patients with IBS were asymptomatic or had very mild symptoms (IBS-SSS <150) and 19 were excluded as they had one or more of the exclusion criteria. Five patients who underwent screening and randomisation did not attend to receive the first dose of study medication. As these patients did not receive any study treatment and blinding was not compromised, their study numbers were reallocated (Figure 1). Of the 186 patients, 54 were already gastroenterology out-patients of Kings College Hospital, 110 were...
new referrals from primary care and 22 were primary care patients who responded to a study invite letter.

One hundred and eighty-six patients were randomised to receive study medication. Demographic details and IBS related summary measures are shown in Table 1.

A total of 152 (81.7%) patients completed the 12 week study; 100 (80.6%) in the probiotic group and 52 (83.9%) in the placebo group. Compliance with study medication was high with the vast majority of patients missing none or less than one dose of medication per week. Thirty four patients withdrew from the study during the treatment phase; 24 (19.4%) who received the probiotic and 10 (16.1%) who received the placebo. A further 14 patients were lost during the follow-up period, 7 (5.6%) from the probiotic group and 7 (11.3%) from the placebo group. Pearson’s chi-squared analysis showed that there was no difference in the number of withdrawals between the two groups at week 12 (P = 0.69) or week 16 (P = 0.73).

Table 2 (ITT LOCF analyses) and 3 (PP analyses) show the overall results. There were no major differences between the two methodological outcomes. Table 2 shows that there was a mean reduction of IBS-SSS of –63.3 in the probiotic group from baseline to week 12 compared with –28.3 in the placebo group in the ITT analysis. This primary end-point, mean difference in the change in IBS-SSS between the two groups, was statistically significant in favour of the probiotic group; the estimated difference was –35.0 (95% CI: –62.03, –7.87) (P = 0.01). There were no significant differences between the two groups during the treatments at weeks 4 and 8. Figure 2 shows the changes in the IBS-SSS at each interval during the study.

Tables 2 and 3, also show the change in individual component scores for IBS-SSS, the mean differences for the component scores for pain and bowel habit satisfaction were statistically significant in favour of the probiotic group while those for bloating and QOL were not significant. Furthermore, there were no significant differences between the mean changes in IBS-QOL scores between patients taking probiotic and placebo at 12 weeks or at the earlier interval time points (weeks 4 and 8).

An exploratory post hoc sub-group analysis was undertaken on patients with moderate to severe symptoms (IBS-SSS >175) at study entry (96% of the study cohort) to assess if there was a difference in the number of patients achieving symptom relief (mild or no symptoms) at the end of the 12 week treatment period. This showed a trend in favour of the probiotic, although the difference between the two groups was not statistically significant (P = 0.06) with 33 patients (26.6%) in the treatment group, vs. 9 (14.5%) in the placebo group reporting mild or no symptoms at week 12.

A further exploratory post hoc analysis was conducted to look at those patients that achieved a MCID at week 12. If the MCID is considered as a change of ≥50 points, then there was no difference between the groups; 56 (45.2%) vs. 26 (41.2%) in the probiotic and placebo groups respectively (P = 0.76). If the MCID is considered as a change of ≥95 points then there is a statistically significant difference between the groups in favour of the probiotic; 39 (31.5%) vs. 9 (14.5%) in the probiotic and placebo groups respectively (P = 0.01).

An ordinary linear regression model was fitted to the IBS-SSS at week 12; results of the estimated regression coefficient showed a mean difference of 40.8 (95% CI: 4.64, 76.99) between the probiotic and placebo group (P = 0.027). After adjustment for baseline symptom severity (IBS-SSS), the difference remained statistically significant with a regression coefficient of 39.2 (CI: 9.94, 68.42) and a P value of 0.009; smaller than for the unadjusted model. While the magnitude of difference is almost the same there is a narrower confidence interval (CI). Further adjustments for age at baseline were also conducted but did not alter the regression coefficient or the level of significance of the difference between the IBS-SSS in the two groups. Residuals were examined and

### Table 1 | Patient baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>Probiotic (n = 124)</th>
<th>Placebo (n = 62)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age [years; mean (±s.d.)]</td>
<td>39.1 (10.5)</td>
<td>36.8 (10.8)</td>
</tr>
<tr>
<td>Sex [female (%); male (%)]</td>
<td>84 (67.8); 40 (32.3)</td>
<td>45 (72.6); 17 (27.4)</td>
</tr>
<tr>
<td>Mean IBS-SSS [mean (±s.d.)]</td>
<td>304 (67.8)</td>
<td>306 (80.3)</td>
</tr>
<tr>
<td>Mean IBS-QOL [mean (±s.d.)]</td>
<td>68 (27.1)</td>
<td>72 (27.5)</td>
</tr>
<tr>
<td>IBS disease duration [years, n (%)]</td>
<td>10 (8.1)</td>
<td>3 (4.8)</td>
</tr>
<tr>
<td>≤1</td>
<td>62 (50.0)</td>
<td>34 (54.8)</td>
</tr>
<tr>
<td>&gt;5</td>
<td>52 (41.9)</td>
<td>25 (40.3)</td>
</tr>
<tr>
<td>IBS subtype by predominant bowel habit, n (%)</td>
<td>48 (38.7)</td>
<td>22 (35.5)</td>
</tr>
<tr>
<td>Diarrhoea (IBS-D)</td>
<td>31 (25.0)</td>
<td>9 (14.5)</td>
</tr>
<tr>
<td>Constipation (IBS-C)</td>
<td>38 (30.7)</td>
<td>28 (45.2)</td>
</tr>
<tr>
<td>Unclassified (IBS)</td>
<td>7 (5.65)</td>
<td>3 (4.8)</td>
</tr>
</tbody>
</table>

IBS, irritable bowel syndrome; SSS, symptom severity score; QOL, quality of life; s.d., standard deviation.
found to be complying with the normality assumed for linear regression. A comparison of the results from the PP analysis and the ITT analysis was made as a simple sensitivity analysis of the LOCF method. There were no major differences between the two analyses with a slightly smaller magnitude of difference in the ITT cohort (−35.0, 95% CI −62.03 to −7.87) than in the PP cohort (−33.0, 95% CI −68.24 to −9.66) but with a narrower CI. Both analyses had similar P values.

One hundred and thirty-eight (74.2%) patients, 93 (75%) and 45 (72.6%) who had received the probiotic and 45 (72.6%) who had received placebo, were included in the follow-up analysis at week 16. Results showed no significant differences between the two groups at this time; mean change in total IBS-SSS for the probiotic −53.8 vs. placebo −57.2; mean difference 3.4 (95% CI, −30.17, 37.02), P = 0.84. While the response in the probiotic group was maintained 4 weeks after stopping the treatment, there was an increase in response in the placebo group.

Both treatments were well tolerated. A total of 35 adverse events were reported in the probiotic group (five patients withdrew from the study) compared with 19 (one patient withdrew from the study) in the placebo group; bloating and change in bowel habit were the most frequently reported adverse events; no serious adverse events were reported during the study (Table 4).

The overall mean (±s.d.) urinary excretion of lactulose/1-rhamnose was 0.03 ± 0.02 from the whole group of patients and did not differ significantly (P > 0.9) between patients going on to the probiotic (0.03 ± 0.02) and placebo (0.03 ± 0.02), with one patient in each group having values above the upper normal range of 0.06.

Similarly, most patients had faecal calprotectin values within the normal range (<50 mg/L). In the whole cohort the mean value of faecal calprotectin (whole group 33.1 ± 73.5) did not differ significantly (P = 0.57) between patients receiving the probiotic (35.2 ± 89.3 mg/L) and placebo (29.1 ± 49.8 mg/L). Twenty two patients had calprotectin levels above the upper limit of the reference range. Neither the probiotic [calprotectin 111.9 ± 62.5 and 66.6 ± 49.8 mg/L pre- and post-treatment (P = 0.18)] nor placebo [118.4 ± 48.7 and 106.8 ± 194.4 mg/L pre- and post-treatment (P = 0.88)] had a significant effect on the calprotectin concentrations in these patients.
The primary outcome measure showed a highly significant improvement in global symptom severity measures and QOL in patients with IBS over a 12 week treatment duration. Improving global symptom severity measures and QOL in patients with IBS over a 12 week treatment duration would be effective at increasing the overall health status of the patient.24 The reason some patients with IBS have mild intestinal inflammation is unknown. Some patients may be taking over the counter aspirin or NSAIDs, while others may be misusing or sensitive to the intestinal effects of alcohol.32 Consistent with the nature of IBS, the vast majority of patients had normal laboratory findings including; full blood count, liver and renal profiles, ESRs and CRP. Furthermore, only two patients had increased small intestinal permeability, which is in keeping with some32, 33 but not all previous studies.34 Furthermore; faecal calprotectin was raised in less than 15% of patients, again in keeping with previous results.33 The reason some patients with IBS have mild intestinal inflammation is unknown. Some patients may be taking over the counter aspirin or NSAIDs, while others may be misusing or sensitive to the intestinal effects of alcohol.32

Compliance with study medication was high and the majority of patients missed none or less than one dose of medication per week. The adverse events were transient and mild in nature and accounted for only a small minority of the study withdrawals. In addition, there were no serious adverse events suggesting that the probiotic has a good safety profile and is well tolerated in this cohort of patients.

Figure 2 | Mean change in IBS-SSS total score from baseline to week 12 (ITT LOCF analysis). The figure shows mean IBS-SSS values for each study time point and illustrates the decline in IBS-SSS for patients receiving treatment with the probiotic compared to placebo. Week 12 (P = 0.04). The number of patients at week 0 were 124 and 62 for probiotic and placebo, respectively, and 100 and 52 at week 12.
This study did not detect any significant change in the IBS-QOL score between the probiotic and placebo group during the treatment. The use of this robust scoring system for assessing outcomes in IBS treatment trials has been advocated in order to allow a comparison of efficacy between different treatments. The questionnaire

**Table 3 | IBS-SSS and IBS-QOL scores: baseline to week 12 for the PP analysis**

<table>
<thead>
<tr>
<th></th>
<th>Mean baseline (±s.d.)</th>
<th>Mean week 12 (±s.d.)</th>
<th>Mean change (±s.d.) baseline to week 12</th>
<th>Mean difference Probiotic vs. placebo (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IBS-SSS total</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Probiotic</td>
<td>303.6 (67.75)</td>
<td>230.1 (106.86)</td>
<td>−71.0 (88.24)</td>
<td>−39.0 (−68.24, −9.66)</td>
<td>0.01</td>
</tr>
<tr>
<td>Placebo</td>
<td>306 (80.31)</td>
<td>270.9 (103.51)</td>
<td>−32.0 (80.88)</td>
<td></td>
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<tr>
<td>IBS-SSS pain</td>
<td></td>
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<tr>
<td>Probiotic</td>
<td>106.3 (40.63)</td>
<td>77.7 (56.58)</td>
<td>−27.2 (47.64)</td>
<td>−17.0 (−32.99, −1.05)</td>
<td>0.04</td>
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<tr>
<td>Placebo</td>
<td>111.7 (42.31)</td>
<td>102.5 (54.08)</td>
<td>−10.1 (46.21)</td>
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<tr>
<td>IBS-SSS bloating</td>
<td></td>
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<td></td>
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<tr>
<td>Probiotic</td>
<td>73.8 (18.52)</td>
<td>46.2 (29.02)</td>
<td>−10.4 (23.59)</td>
<td>−5.2 (−13.33, 3.00)</td>
<td>0.21</td>
</tr>
<tr>
<td>Placebo</td>
<td>68.4 (21.23)</td>
<td>46.8 (28.39)</td>
<td>−5.2 (24.04)</td>
<td></td>
<td></td>
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<tr>
<td>IBS-SSS bowel habit</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Probiotic</td>
<td>53.4 (24.39)</td>
<td>55.9 (23.75)</td>
<td>−17.4 (23.31)</td>
<td>−11.4 (−39.24, −3.50)</td>
<td>0.01</td>
</tr>
<tr>
<td>Placebo</td>
<td>54.5 (25.61)</td>
<td>61.8 (17.92)</td>
<td>−6.0 (22.73)</td>
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<tr>
<td>IBS-SSS QOL satisfaction</td>
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</tr>
<tr>
<td>Probiotic</td>
<td>70.2 (17.38)</td>
<td>53.8 (23.57)</td>
<td>−16.0 (20.54)</td>
<td>−5.4 (−11.93, 1.13)</td>
<td>0.10</td>
</tr>
<tr>
<td>Placebo</td>
<td>70.7 (19.90)</td>
<td>59.8 (20.50)</td>
<td>−10.6 (15.79)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IBS-QOL score</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Probiotic</td>
<td>53.2 (20.25)</td>
<td>60.5 (21.56)</td>
<td>9.1 (18.24)</td>
<td>5.8 (−1.40, 12.94)</td>
<td>0.11</td>
</tr>
<tr>
<td>Placebo</td>
<td>50.7 (19.93)</td>
<td>54.7 (20.53)</td>
<td>7.7 (19.13)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

IBS-SSS, irritable bowel syndrome symptom severity score; QOL, quality of life; s.d., standard deviation.

Per-protocol analyses shows that the difference in the change in mean overall IBS-SSS score was statistically significant implying a beneficial action of the probiotic over placebo. This occurred mainly because of improvements in abdominal pain scores and patients’ perceived satisfaction with their bowel habits. However, measures of QOL did not show any statistical difference between probiotic and placebo.

This study did not detect any significant change in the IBS-QOL score between the probiotic and placebo group during the treatment. The use of this robust scoring system for assessing outcomes in IBS treatment trials has been advocated in order to allow a comparison of efficacy between different treatments. The questionnaire

**Table 4 | Adverse events and withdrawals**

<table>
<thead>
<tr>
<th>Event</th>
<th>Probiotic, n = 124 (%)</th>
<th>Probiotic withdrawals</th>
<th>Placebo, n = 62 (%)</th>
<th>Placebo withdrawals</th>
<th>Total with event (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>5 (4)</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>5 (2.7)</td>
</tr>
<tr>
<td>Intolerant to taste</td>
<td>1 (0.8)</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1 (0.5)</td>
</tr>
<tr>
<td>Weight gain</td>
<td>1 (0.8)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 (0.5)</td>
</tr>
<tr>
<td>Change in bowel habit</td>
<td>6 (4.8)</td>
<td>1 (diarrhoea)</td>
<td>6 (9.6)</td>
<td>1 (constipation)</td>
<td>12 (6.5)</td>
</tr>
<tr>
<td>Bloating</td>
<td>10 (8.1)</td>
<td>2 (3.2)</td>
<td>12 (6.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heartburn/dyspepsia</td>
<td>3 (2.4)</td>
<td>1 (1.6)</td>
<td>4 (2.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain</td>
<td>3 (2.4)</td>
<td>1</td>
<td>7 (3.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>2 (1.6)</td>
<td>1</td>
<td>3 (1.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acne</td>
<td>1 (0.8)</td>
<td>1 (1.6)</td>
<td>2 (1.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>1 (0.8)</td>
<td>1 (1.6)</td>
<td>2 (1.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vaginal candida</td>
<td>1 (0.8)</td>
<td>0</td>
<td>1 (0.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flatulence</td>
<td>2 (1.6)</td>
<td>1</td>
<td>3 (1.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Halitosis</td>
<td>0</td>
<td>1 (1.6)</td>
<td>1 (0.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>0</td>
<td>1 (1.6)</td>
<td>1 (0.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total no of episodes</td>
<td>35 (28.2)</td>
<td>5</td>
<td>19 (30.6)</td>
<td>1</td>
<td>54 (29.0)</td>
</tr>
<tr>
<td>Total number experiencing adverse events</td>
<td>33 (26.6)</td>
<td>14 (22.6)</td>
<td>47 (25.3)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The reported adverse events were generally mild and comparable between treatments (bloating and nausea being somewhat more prevalent with the probiotic).
covers many aspects of the disease as well as emotional and social issues and it is noteworthy that although some randomised placebo controlled trials show a significant improvement in the various symptom scores following administration of different probiotics, these have not demonstrated a significant improvement in the IBS-QOL scores, similar to the present study.

A criticism of our study could be the changes in protocol that took place prior to study start. These were largely the result of a desire to ensure that this early study measured any potential effects of the probiotic in an appropriate and robust way. We deliberately included all subtypes of IBS as many patients classified as diarrhoea predominant, or alternatively constipation predominant, can change classification from one clinic visit to the next. Recent studies confirm that most IBS patients change subtype over time and suggest that a consistent stool pattern sub-classification requires a 2 week assessment.

The improvement in the IBS-SSS in this study is similar to some other probiotic studies although not all, with different beneficial effects on the composites of the score with different probiotics. Collectively this is indicative of the efficacy of probiotics in IBS. Of note however, is the diversity of the probiotic preparations available, which range from fermented milk products to lyophilised forms containing both single and multiple strains of different bacteria. In addition, there are large variations in study design and quality of these studies. For example, different studies may use different symptom scores, some studies only include one sub-type of the IBS population (constipation or diarrhoea predominant), the length of treatment varies as does the dosage, strengths and type of probiotic used. As a result of these heterogeneities, any comparison of randomised controlled trials (RCTs) of probiotics in IBS is difficult. The majority of RCTs that have been undertaken for probiotics in IBS have reported on small numbers of patients; only three and four included more than 100 patients in meta-analyses by Hoveyda and McFarland, respectively. In both of these analyses, many of the RCTs included were not considered of good methodological quality; in the McFarland analysis only eight of the 20 studies scored more than four in the Linde assessment and in the Hoveyda analysis, on a scale of 0–4, seven scored 2 or less. Examples from the largest RCT of probiotics in IBS to date highlight these issues of rigour. This was a multicentre study of a single strain product (encapsulated *Bifidobacterium infantis* 35624), which recruited over 300 female patients with a diagnosis of IBS (Rome II criteria) and these were split into three dosage groups and a placebo group. After 4 weeks of treatment, there was a statistically significant improvement in the primary end-point, in one dosage group compared with placebo ($P = 0.023$) and a 20% greater improvement in subject global assessment in one treatment group compared with placebo ($P < 0.02$). The study design excluded patients with severe pain scores however, and used a composite symptom score that is not as yet widely used and not validated.

Despite these limitations there is accumulating evidence that certain probiotics may have an important role in IBS and a recent systematic review concluded, with a high level of evidence, that specific probiotics help reduce overall symptom burden and abdominal pain in IBS.

This study deliberately utilised independently designed and validated instruments to assess symptom severity (IBS-SSS) and QOL specific to IBS patients in order to facilitate comparison with future studies. Furthermore, it has been our intention throughout, to conduct this study to the same rigorous methodological and reporting standards applied to clinical trials for new drug treatments. Our results show that this multi-strain probiotic is safe, well tolerated and efficacious in improving symptom severity in patients with IBS, which adds further weight to the concept of probiotic treatment in patients with IBS. IBS is a very complex condition with a wide range of contributing environmental factors. Thus, a multidisciplinary approach to treatment is essential for optimising outcomes. It seems increasingly likely that certain probiotics such as Symprove may play a significant role in the overall management of IBS. Nevertheless, our study may be limited by the study size, its single-centre design and should be followed up with a larger multi-centre trial.

**AUTHORSHIP**

Guarantor of the article: Prof. Ingvar Bjarnason.

*Author contributions*: GS and IB contributed to study design, recruitment, enrolment and assessment of participants, data collection analysis. SA and RS contributed to study design and analysis. RS managed all aspects of laboratory support. All authors contributed to writing the manuscript and approved the final version of the manuscript.

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